314.

Notice of Allowability	Application No.	Applicant(s)	
	09/941,882	WILLIAMS ET AL.	
	Examiner	Art Unit	
	Jezia Riley	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *Amdt filed 10/30/03*.
2. ☒ The allowed claim(s) is/are *33-53*.
3. ☐ The drawings filed on _____ are accepted by the Examiner.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.
5. ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
   (a) ☐ The translation of the foreign language provisional application has been received.
6. ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application. **THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

7. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
8. ☒ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No. ____.
   (b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the Examiner.
   (c) ☒ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No. 11/03.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the margin according to 37 CFR 1.121(d).

9. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1☐ Notice of References Cited (PTO-892)
2☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No. _____
4☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5☐ Notice of Informal Patent Application (PTO-152)
6☐ Interview Summary (PTO-413), Paper No._____ .
7☒ Examiner's Amendment/Comment
8☐ Examiner's Statement of Reasons for Allowance
9☐ Other .

DETAILED ACTION

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

The application has been amended as follows:

This application is in condition for allowance except for the presence of claims 31-32 non-elected without traverse.

Accordingly, **claims 31-32 have been cancelled.**

Additionally, the formal drawings are required.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jezia Riley whose telephone number is 703-305-6855. The examiner can normally be reached on 9:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 703-308-1119. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Tuesday, November 25, 2003

JEZIA RILEY
PRIMARY EXAMINER

ALLOWED CLAIMS/ TJ

33. (New): A method of DNA sequencing comprising the steps of:

(a) providing a template system comprising at least one nucleic acid molecule of unknown sequence hybridized to a primer oligonucleotide in the presence of a DNA polymerase with reduce exonuclease activity;

(b) contacting the template system with a single type of deoxyribonucleotide under conditions which allow extension of the primer by incorporation of at least one deoxyribonucleotide having a fluorescent moiety to the 3' end of the primer to form an extended primer;

(c) detecting whether extension of the primer has occurred by detecting a fluorescent signal emitted by the fluorescent moiety, and further comprising destroying the fluorescent signal without removal of the fluorescent moiety;

(d) detecting the number of deoxyribonucleotides incorporated into the primer;

(e) removing unincorporated deoxyribonucleotide; and

(f) repeating steps (a) through (e) to determine the nucleotide sequence of the nucleic acid molecule.

34. (New): The method of claim 33 wherein the fluorescent moiety is destroyed by reaction with compounds capable of extracting an electron from the excited state of the fluorescent moiety.

35. (New): The method of claim 34 wherein the compound is a diphenyliodonium salt.

36. (New): A method of DNA sequencing comprising the steps of:

(a) providing a template system comprising at least one nucleic acid molecule of unknown sequence hybridized to a primer oligonucleotide in the presence of a DNA polymerase with reduced exonuclease activity;

(b) contacting the template system with a single type of deoxyribonucleotide under conditions which allow extension of the primer by incorporation of at least one deoxyribonucleotide to the 3' end of the primer to form an extended primer;

(c) detecting whether extension of the primer has occurred by detecting a change in the concentration of unincorporated deoxyribonucleotide;

(d) detecting the number of deoxyribonucleotides incorporated into the primer;

(e) removing unincorporated deoxyribonucleotide; and

(f) repeating steps (a) through (e) to determine the nucleotide sequence of the nucleic acid molecule.

37. (New): A method of DNA sequencing comprising the steps of:

(a) providing a template system comprising at least one nucleic acid molecule of unknown sequence hybridized to a primer oligonucleotide in the presence of a DNA polymerase with reduced exonuclease activity;

(b) contacting the template system with a single type of deoxyribonucleotide under conditions which allow extension of the primer by incorporation of at least one deoxyribonucleotide having the capability of generating heat to the 3' end of the primer to form an extended primer;

(d) detecting whether extension of the primer has occurred by detecting the heat generated by incorporating the deoxyribonucleotides having the capability to generate heat;

(d) detecting the number of deoxyribonucleotides incorporated into the primer;

(e) removing unincorporated deoxyribonucleotide; and

(f) repeating steps (a) through (e) to determine the nucleotide sequence of the nucleic acid molecule.

38. (New): The method of claim 37 wherein a thermopile is used to detect the generated heat.

39. (New): The method of claim 37 wherein a thermistor is used to detect the generated heat.

40. (New): A method of DNA sequencing comprising the steps of:

(a) providing a template system comprising a buffer and at least one nucleic acid molecule of unknown sequence hybridized to a primer oligonucleotide in the presence of a DNA polymerase with reduced exonuclease activity;

(b) contacting the template system with a single type of deoxyribonucleotide under conditions which allow extension of the primer by incorporation of at least one deoxyribonucleotide which generates heat that is absorbed by the buffer to the 3' end of the primer to form an extended primer;

(c) detecting whether extension of the primer has occurred by measuring the refractive index of the buffer;

(d) detecting the number of deoxyribonucleotides incorporated into the primer;

(e) removing unincorporated deoxyribonucleotide; and

(f) repeating steps (a) through (e) to determine the nucleotide sequence of the nucleic acid molecule.

41. (New): A method of DNA sequencing comprising the steps of:

(a) providing a template system comprising at least one nucleic acid molecule of unknown sequence hybridized to a primer oligonucleotide in the presence of a DNA polymerase with reduced exonuclease activity;

(b) contacting the template system with a single type of deoxyribonucleotide under conditions which allow extension of the primer by incorporation of at least one deoxyribonucleotide to the 3' end of the primer to form an extended primer;

(c) detecting whether extension of the primer has occurred by detecting the concentration of pyrophosphate release by addition of the deoxyribonucleotide to the 3' end of the primer where the concentration of pyrophosphate is detected by hydrolyzing the pyrophosphate and measuring heat generated by hydrolysis of the pyrophosphate;

(d) detecting the number of deoxyribonucleotides incorporated into the primer;

(e) removing unincorporated deoxyribonucleotide; and

(f) repeating steps (a) through (e) to determine the nucleotide sequence of the nucleic acid molecule.

42. (New): A method of DNA sequencing comprising the steps of:

(a) providing a template system comprising at least one nucleic acid molecule of unknown sequence hybridized to a primer oligonucleotide in the presence of a DNA polymerase with reduced exonuclease activity wherein the DNA polymerase is a T4 DNA polymerase with a substitution of amino acid residue Asp112 by Ala and Glu114 by Ala;

(b) contacting the template system with a single type of deoxyribonucleotide under conditions which allow extension of the primer by incorporation of at least one deoxyribonucleotide to the 3' end of the primer to form an extended primer;

(c) detecting whether extension of the primer has occurred;

(d) detecting the number of deoxyribonucleotides incorporated into the primer;

(e) removing unincorporated deoxyribonucleotide; and

(f) repeating steps (a) through (e) to determine the nucleotide sequence of the nucleic acid molecule.

43. (New): The method of claim 40 wherein the DNA polymerase further comprises a T4 DNA polymerase with a substitution of amino acid residue Ile417 by Val.

44. (New): A method of DNA sequencing comprising the steps of:

(a) providing a template system comprising at least one nucleic acid molecule of unknown sequence hybridized to a primer oligonucleotide in the presence of an exonuclease deficient DNA polymerase;

(b) contacting the template system with a single type of deoxyribonucleotide under conditions which allow extension of the primer by incorporation of at least one deoxyribonucleotide having a fluorescent moiety to the 3' end of the primer to form an extended primer;

(c) detecting whether extension of the primer has occurred by detecting a fluorescent signal emitted by the fluorescent moiety and destroying the fluorescent signal without removal of the fluorescent moiety thereby identifying the deoxyribonucleotide added to the 3' end of the primer;

(d) detecting the number of deoxyribonucleotides incorporated into the primer;

(e) removing unincorporated deoxyribonucleotide;

(f) contacting the template system with a mixture including an exonuclease proficient DNA polymerase, an exonuclease deficient DNA polymerase and the identified deoxyribonucleotide of step (b);

(g) removing the mixture of step (f); and

(h) repeating steps (a) through (g) to determine the nucleotide sequence of the nucleic acid molecule.

45. (New): The method of claim 44 wherein the fluorescent moiety is destroyed by reaction with compounds capable of extracting an electron from the excited state of the fluorescent moiety.

46. (New): The method of claim 45 wherein the compound is a diphenyliodonium salt

47. (New): A method of DNA sequencing comprising the steps of:

(a) providing a template system comprising at least one nucleic acid molecule of unknown sequence hybridized to a primer oligonucleotide in the presence of an exonuclease deficient DNA polymerase;

(b) contacting the template system with a single type of deoxyribonucleotide under conditions which allow extension of the primer by incorporation of at least one deoxyribonucleotide capable of generating heat to the 3' end of the primer to form an extended primer;

(c) detecting whether extension of the primer has occurred by detecting heat generated by incorporating the at least one deoxyribonucleotide thereby identifying the deoxyribonucleotide added to the 3' end of the primer;

(d) detecting the number of deoxyribonucleotides incorporated into the primer;

(e) removing unincorporated deoxyribonucleotide;

(f) contacting the template system with a mixture including an exonuclease proficient DNA polymerase, and exonuclease deficient DNA polymerase and the identified deoxyribonucleotide of step (b);

(g) removing the mixture of step (f); and

(h) repeating steps (a) through (g) to determine the nucleotide sequence of the nucleic acid molecule.

48. (New): The method of claim 47 wherein a thermopile is used to detect the generated heat.

49. (New): The method of claim 47 wherein a thermistor is used to detect the generated heat.

50. (New): A method of DNA sequencing comprising the steps of:

(a) providing a template system comprising a buffer and at least one nucleic acid molecule of unknown sequence hybridized to a primer oligonucleotide in the presence of an exonuclease deficient DNA polymerase;

(b) contacting the template system with a single type of deoxyribonucleotide under conditions which allow extension of the primer by incorporation of at least one deoxyribonucleotide capable of generating heat which is absorbed by the buffer to the 3' end of the primer to form an extended primer;

(c) detecting whether extension of the primer has occurred by measuring the refractive index of the buffer thereby identifying the deoxyribonucleotide added to the 3' end of the primer;

(d) detecting the number of deoxyribonucleotides incorporated into the primer;

(e) removing unincorporated deoxyribonucleotide;

(f) contacting the template system with a mixture including an exonuclease proficient DNA polymerase, an exonuclease deficient DNA polymerase and the identified deoxyribonucleotide of step (b);

(g) removing the mixture of step (f); and

(h) repeating steps (a) through (g) to determine the nucleotide sequence of the nucleic acid molecule.

51. (New): A method of DNA sequencing comprising the steps of:

(a) providing a template system comprising at least one nucleic acid molecule of unknown sequence hybridized to a primer oligonucleotide in the presence of an exonuclease deficient DNA polymerase;

(b) contacting the template system with a single type of deoxyribonucleotide under conditions which allow extension of the primer by

incorporation of at least one deoxyribonucleotide to the 3' end of the primer to form an extended primer;

(c) detecting whether extension of the primer has occurred by detecting the concentration of pyrophosphate released by incorporation of a deoxyribonucleotide to the 3' end of the primer where the concentration of pyrophosphate is detected by hydrolyzing the pyrophosphate and measuring the heat generated by hydrolysis of the pyrophosphate thereby identifying the deoxyribonucleotide added to the 3' end of the primer;

(d) detecting the number of deoxyribonucleotides incorporated into the primer;

(e) removing unincorporated deoxyribonucleotide;

(f) contacting the template system with a mixture including an exonuclease proficient DNA polymerase, an exonuclease deficient DNA polymerase and the identified deoxyribonucleotide of step (b);

(g) removing the mixture of step (f); and

(h) repeating steps (a) through (g) to determine the nucleotide sequence of the nucleic acid molecule.

52. (New): The method of claim 50 wherein the exonuclease deficient DNA polymerase further comprises a T4 DNA polymerase with a substitution of amino acid residue Ile417 by Val.

53. (New): A method of DNA sequencing comprising the steps of:

(a) providing a template system comprising at least one nucleic acid molecule of unknown sequence hybridized to a primer oligonucleotide in the presence of an exonuclease deficient DNA polymerase wherein the exonuclease deficient DNA polymerase is a T4 DNA polymerase with a substitution of amino acid residue Asp112 by Ala and Glu114 by Ala;

(b) contacting the template system with a single type of deoxyribonucleotide under conditions which allow extension of the primer by incorporation of at least one deoxyribonucleotide to the 3' end of the primer to form an extended primer;

(c) detecting whether extension of the primer has occurred thereby identifying the deoxyribonucleotide added to the 3' end of the primer;

(d) detecting the number of deoxyribonucleotides incorporated into the primer;

(e) removing unincorporated deoxyribonucleotide;

(f) contacting the template system with a mixture including an exonuclease proficient DNA polymerase, an exonuclease deficient DNA polymerase and the identified deoxyribonucleotide of step (b);

(g) removing the mixture of step (f); and

(h) repeating steps (a) through (g) to determine the nucleotide sequence of the nucleic acid molecule.